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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,001	07/19/2004	Nisar P Malek	14538A-006610US	6809

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/502,001	MALEK ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *10-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *N/A* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group II, claims 1-9 in the reply filed on 05/15/2006 is acknowledged. The traversal is on the ground(s) that the MPEP does not specify that the category combinations set forth at page 3 of the restriction requirement mailed 04/11/2006 are the only category combinations permitted (see MPEP 1850). This is not found persuasive because 37 CFR 1.475 (b) states that an international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or
(2) A product and a process of use of said product; or
(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
(4) A process and an apparatus or means specifically designed for carrying out the said process; or
(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

SDP 6/7/06

Groups I-VI are drawn to structurally distinct products. Groups VII-X are drawn to different methods of making the different products of Groups III-VI. The methods do not relate to the elected Group II.

The requirement is still deemed proper and is therefore made FINAL.

It is noted that claim 1 is examined as it reads on the elected invention wherein the mutant p27 gene is located at the endogenous $p27^{Kip1}$ locus. In light of this interpretation of the claim, claims 4 and 5 are of the same scope as claim 1. If claim 1 is amended to read on the elected invention, then claims 4 and 5 will fail to further limit the parent claim.

Specification

The disclosure is objected to because of the following informalities: The priority information should be listed in the first line of the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated heterozygous transgenic somatic cell or isolated transgenic mouse somatic cell, primordial germ cell, oocyte, egg, spermatocyte, sperm cell, fertilized egg, zygote or embryonic stem cell having a mutant p27 gene lacking a Cdk2 phosphorylation site located at the endogenous $p27^{Kip1}$ locus, wherein the mutant p27 gene encodes a mutant $p27^{Kip1}$ polypeptide having a longer half-life in S phase that wildtype $p27^{Kip1}$ polypeptide, does not reasonably provide enablement for a non-mouse homozygous somatic cell or any non-mouse primordial germ cell, oocyte, egg, spermatocyte, sperm cell, fertilized egg, zygote or embryonic stem cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims broadly encompass any species of isolated primordial germ cell, oocyte, egg, spermatocyte, sperm cell, fertilized egg, zygote or embryonic stem cell comprising a gene-targeted insertion at the $p27^{Kip1}$ locus. The specification fails to teach how to make any of these cells in vitro such that homologous recombination occurs resulting in these cell types having a gene-targeted insertion or replacement as required by the elected invention. The only means known to the skilled artisan to obtain an oocyte or sperm cell comprising the claimed genetic alteration is by isolating it from a live animal. However, at the time of filing the only species for which a gene-targeting event can be passed on to a live animal is in mouse because gene-targeting has not been demonstrated in any totipotent cell, capable of giving rise to an animal, other than mouse ES cells. Homlogous recombination occurs at such a low frequency that cell

division and selection must occur to identify homologous recombination events as opposed to random genomic insertions.

The art at the time of filing held that totipotent ES cells capable of giving rise to a germ-line transgenic animal were not available for any species other than mouse. Campbell and Wilmut (1997, **Theriogenology**, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65). Wheeler (2001, **Theriogenology**, Vol. 56, 1345-1369) taught putative pig ES cells, which produced pig chimeras but there is no disclosure that the chimera gave rise to a pig of the ES cell phenotype (pages 1351-1352), indicating that the ES cells are not totipotent as they are not germline competent. Further, Wheeler states, in reference to ES cells recently isolated and the production of swine and cattle chimera, "validation of totipotency of these embryo-derived ES cell lines awaits confirmation" (page 1351, parag. 1, last sentence). Prelle (1999, **Cells Tissues Organs**, Vol. 165, pages 220-236) states many embryo-derived cell lines resemble morphologically mouse ES cells, and have the ability to differentiate in vitro, but there is no evidence of live born, fertile germ line chimeras in species other than mouse (page 222, col. 2, parag. 1, lines 10-16).

The specification has contemplated use of somatic cell nuclear transfer in making animals comprising the claimed gene-targeted alteration, which would provide a source of the claimed isolated primordial germ cells, oocyte, egg, spermatocyte, sperm cell, fertilized egg, and zygotes. However, it is noted that at the time of filing, this technology was highly underdeveloped. Thomson *et al.* [**Reprod. Supp.**, 61:495-508, 2003] review the state of the art of gene targeting in somatic cells for use in nuclear transfer methodologies and state that procedures to enhance

the lifespan of targeted somatic cells *in vitro* are needed. In particular, Thomson states that premature senescence often occurs, which makes it difficult to confirm a targeting event in somatic cells and that cloning efficiency has been negatively correlated with passage number. See p. 501. The inefficiency and unpredictability of homologous recombination in somatic cells is supported by Polejaeva and Campbell [**Theriogenology**, 53:117-126, 2000] who teach that gene targeting in somatic cells is unpredictable because of the lower frequency of homologous recombination than ES cells, and a finite capacity for number of cell divisions.

Furthermore, the specification has not contemplated a use for the claimed primordial germ cells, an oocyte, an egg, spermatocyte, sperm cell, fertilized egg, zygote or ES cells other than in making an animal. Thus, with specific respect to ES cells that exist and can be selected in culture, because they are not useful in making an animal with the exception of mouse ES cells, one of skill in the art would not know how to use them.

Finally, with respect to homozygous somatic cells encompassed by the claims, homozygous gene-targeting events cannot be made in vitro. Thus an animal would be necessary for homozygous somatic cells encompassed by the claims. In light of the state of the art set forth above, the specification is not enabling for any homozygous cells other than mouse cells.

Thus, because the specification does not teach how to generate a gene targeted alteration in primordial germ cells, an oocyte, an egg, spermatocyte, sperm cell, fertilized egg, zygote in any manner other than isolating them from a gene-targeted animal and because, at the time of filing, non-mouse ES cells capable of contributing to the germ line were not available to make an animal to isolate said cells from, it would require undue experimentation to make the full breadth of cells encompassed by the claims.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is drawn to the transgenic cell of claim 1, comprising progeny of the cell of claim 1. It is unclear how a cell can be itself and its progeny at the same time.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by Malek et al. [IDS, September 2001].

Claims 1-7 and 9 are drawn to isolated cells comprising a mutant p27 gene replacing the endogenous $p27^{Kip1}$ gene wherein the mutant gene lacks a Cdk2 phosphorylation site, leading to

a longer half-life. Claim 2 requires that the mutant $p27^{Kip1}$ inhibit Cdk2 activity. Claim 3 limits the mutation to T187A. Claim 4 requires that the mutant gene be located at the endogenous p27 locus. Claim 5 requires that the cell be either homozygous or heterozygous for the mutant p27 gene. It is noted that the limitations of claims 4 and 5 are moot in light of the elected invention being to the cells having the mutant gene located at the endogenous locus. Claim 6 limits the cell type to a PGC, oocyte, egg, spermatocyte, sperm cell, fertilized egg, or ES cell. Claim 7 limits the cell type to an oocyte, spermatocyte, sperm cell, or fertilized egg. Claim 9 is limited to a somatic cell. Claim 9 limits the cell to a somatic cell. Claim 8 is not included in this rejection because it is unclear what is intended to be claimed (see above).

Malek taught MEF cells isolated from matings of heterozygous $p27^{T187A}$ mice wherein the $p27^{T187A}$ gene replaces the endogenous p27 gene. The resultant embryos from which the cells were obtained are homozygous and heterozygous. The $p27^{T187A}$ half-life was longer during S-phase that $p27^{Kip1}$ (paragraph bridging pages 323-324, page 325, col. 1, para 2). Malek also taught that the mutation does not prevent the Cdk2 inhibitory activation of $p27^{Kip1}$ as required by claim 2 (page 323, col. 1, paragraph 2). Malek taught ES cells, sperm cells, oocytes, and zygotes comprising $p27^{T187A}$ at the $p27^{Kip1}$ locus as Malek et al. taught mice comprising the genetic alteration. Malek et al. created the mice using ES cells comprising the transgenic alteration and subsequent mating of the mice resulted in sperm, oocytes and fertilized eggs having the transgenic alteration (see page 326, col. 1, paragraph 4).

Therefore, Malek at al. taught all of the limitations of claims 1-7 and 9.

Conclusion

It is noted that the restriction requirement has been maintained above. However, the Examiner would consider rejoining certain claims of Group III if limited to a transgenic mouse because the issues regarding the mouse have been fully considered above. Non-mouse species require additional search and consideration that was not carried out for the elected invention and will not be considered for rejoinder.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Valarie Bertoglio
Examiner
Art Unit 1632